REMARKS

Status of the Claims

Applicants note the withdrawal of the previous objections for various informalities, the rejection under 35 U.S.C. § 112, second paragraph, and the nonstatutory double patenting rejection.

Claim 6 has been amended to correct a typographical error in the word "monoclonal." Therefore, no new matter has been added by amendment.

Claims 1 and 3-6 are pending. Reconsideration of the claims is respectfully requested in view of the following remarks. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Rejection of the Claims Under 35 U.S.C.§102 Should Be Withdrawn

The rejection of claims 1-6 under 35 U.S.C.§102 as being anticipated by Rupp *et al.* (GB 2153830) has been maintained. Applicants respectfully traverse.

An anticipation rejection requires a showing that each limitation of a claim must be found in a single reference, practice, or device. *In re Donohue*, 766 F.2d 531, 534, 226 USPQ 619, 621 (Fed. Cir. 1985). Therefore, to anticipate the present claims a reference would have to disclose, at the minimum, the following elements:

> A method of determining the optimal level of product expression in animal cell culture wherein the concentration of a solute of interest in a culture medium composition for optimal product expression is different than the concentration of said solute in the culture medium composition determined for optimal cell growth, which method comprises:
>
> a) growing the animal cell culture in a culture medium to determine optimal cell growth;
>
> b) varying the concentration of the solute in the culture medium to a concentration above that optimal for cell growth, which concentration is effective to create an environment of solute stress on the cell culture as expressed by an inhibitory effect on cell growth or cell density of said cell culture;

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c) monitoring the product expression as concentration of the solute is varied in the culture medium to determine optimal product expression; and

d) selecting the solute concentration that provides the optimal combination of cell growth and product expression, which allows for optimal productivity.

Such a showing has not been established in the present case because Rupp *et al.* does not disclose, among other things, creating "an environment of solute stress on the cell culture as expressed by an inhibitory effect on cell growth or cell density of said cell culture."

In Applicants' specification, "'solute stress' refers to the addition of solutes in such concentrations, at least above that concentration determined for optimal cell growth, that produce a growth inhibitory effect or reduced final cell density, that is, a growth rate or maximum cell density less than that determined for optimal growth." See page 6, lines 12-18. Nothing in Rupp *et al.* discloses creating an environment of *solute stress* on the cell culture as expressed by an inhibitory effect on cell growth or cell density of said cell culture.

To the contrary, Rupp *et al.* discloses the following:

- That the hypertonic media of their invention "promote protein production *without adversely affecting viability of the cells or their growth rates*." Page 2, lines 24-25 *(emphasis added)*.
- That addition of excess amino acids to the culture medium "*does not alter the viability or rate of cell mitosis of protein producing cells* but does cause increased protein production." Example 1, at page 6, lines 30-32 (emphasis added).
- That "changing the osmolarity of the solution by addition of saline *had no significant effect on the cell growth*." Example 2, at page 7, lines 25-27 (emphasis added).
- That a comparison of the cells per mL of settled capsules in hypertonic and isotonic media (Figure 1) shows that "the hypertonic medium *not only did not hinder hybridoma growth, it may actually have increased the growth rate*" (page 6, lines 58-59, interpreting Figure 1) (emphasis added).

Despite the clear teaching that the cells of Rupp *et al.* did not experience growth inhibition, the present rejection is maintained. This is improper because, as will be explained in

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the following paragraphs, no statement or teaching has been identified to support the Office Action's conclusions regarding Rupp *et al.*

The points of the rejection are addressed as they occur in the Office Action.

1. The Office Action maintains that Rupp *et al.* do "teach stressing the cultured cells by using that hypertonic medium generated by addition of excess amino acids as solutes" and even cites particular portions of the reference for support. Applicants' representative has diligently reviewed each cited portion of Rupp *et al.*, but has been unable to locate support for such a conclusion. For instance, the Office Action asserts that "Rupp *et al.* address the issue regarding adverse effect of hypertonic medium (see page 6, lines 58-59)...." However, the cited portion of the reference does not address an adverse effect. To the contrary, the cited text states that "the hypertonic medium *not only did not hinder hybridoma growth, it may actually have increased the growth rate*" (emphasis added). In other words, the cited portion discusses a *positive* effect, not an adverse effect. Moreover, the conclusion Rupp *et al.* reached is that cellular growth was *not* inhibited. Accordingly, Rupp *et al.* do not disclose creating "an environment of solute stress on the cell culture as expressed by an inhibitory effect on cell growth or cell density of said cell culture."

2. The Office Action states that "Rupp *et al.* teach a method of improving or promoting protein production, especially antibody production, in animal cultures rather than targets simply on increasing cell viability...." Whether or not Rupp *et al.* teaches a method of improving or promoting protein production is irrelevant to the inquiry of whether the reference discloses creating "an environment of solute stress on the cell culture as expressed by an inhibitory effect on cell growth or cell density of said cell culture."

3. In the previous amendment, Applicants stated that "[n]owhere does the Rupp *et al.* reference propose or even suggest that one can determine the optimal level of product expression by systematically increasing the level of solute in the culture medium and monitoring product expression to determine the solute concentration at which cell growth becomes inhibited

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but product expression is at its highest." The present Office Action states that this is not persuasive. Specifically, the Office Action asserts that Table 4 teaches that "when reaching a certain level of hypertonicity, the hybidoma cell growth is impaired...." Applicants disagree.

Table 4 demonstrates antibody production, as Rupp *et al.* state in their own summary. See Example 2. Consequently, the data presented in Table 4 does not relate to cell growth and is irrelevant to the present inquiry. The pertinent data, i.e., data related to the growth of the cell cultures referred to in Table 4, is set forth in *Figure 4*. As summarized by Rupp *et al.*, Figure 4 demonstrates that "changing the osmolarity of the solution by addition of saline *had no significant effect on the cell growth*." Example 2 (emphasis added). Consequently, this portion of Rupp *et al.* fails to disclose creating "an environment of solute stress on the cell culture as expressed by an inhibitory effect on cell growth or cell density of said cell culture."

4. The Office Action asserts that Figure 3 compares "stressed cell culture 390" and "unstressed culture 397" and shows "a remarked change in the antibody production by comparison" of these two cultures. Whether or not Figure 3 shows a change in antibody production is irrelevant to the inquiry of whether or not Rupp *et al.* discloses creating "an environment of solute stress on the cell culture as expressed by an inhibitory effect on cell growth or cell density of said cell culture." Further, as already indicated above, Rupp *et al.* conclude that there was no inhibitory effect upon cell growth during the course of the experiments underlying Figure 3. (See Figure 1 of Rupp *et al.*)

After careful study, it is clear that Rupp *et al.* interpreted their data and reached conclusions directly contrary to the conclusions presented in the Office Action regarding the teachings of that reference. Applicants request that if the Examiner has personal knowledge to support conclusions counter to those Rupp *et al.* reached regarding their work that it be presented in an affidavit under 37 CFR §1.104(d)(2), as required.

To summarize, the Patent Office has the burden of demonstrating a sound basis for believing the claimed invention and the prior art are the same; the burden of showing that they do not only shifts to the applicant when such basis is established. *See In re Spada*, 911 F.2d 705,

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15 U.S.P.Q.2d 1655 (Fed. Cir. 1990) (discussing product claims). In the present case, the evidence of record demonstrates that Rupp *et al.* did not disclose a method that includes creating "an environment of solute stress on the cell culture as expressed by an inhibitory effect on cell growth or cell density of said cell culture." Accordingly, this rejection of the claims should be withdrawn.

CONCLUSION

In view of the aforementioned amendments and remarks, Applicants respectfully submit that the rejection of the claims under 35 U.S. C. §102 is overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the US Patent and Trademark Office at Fax No. 703-872-9306 on the date shown below.

Pamela Lockley — July 25, 2003
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